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     FILE 'HCAPLUS' ENTERED AT 15:31:45 ON 23 JUN 2005
L1            1 (GB99-17793 OR WO2000-GB2903#)/AP,PRN

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     FILE 'HCAPLUS' ENTERED AT 15:32:00 ON 23 JUN 2005
L2              TRA L1 1- RN :       65 TERMS

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L3           65 SEA L2

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L4            1 (GB99-17793 OR WO2000-GB2903#)/AP,PRN

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L1   ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2005 ACS on STN
AN   2001:101167  HCAPLUS
DN   134:168315
ED   Entered STN:  09 Feb 2001
TI   Enhancement of bioavailability of peptides with bile salts
IN   Morrison, James Duncan; Lucas, Michael Leslie; Wheeler, Sarah
PA   The University Court of the University of Glasgow, UK
SO   PCT Int. Appl., 28 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
IC   ICM  C07J
CC   63-5 (Pharmaceuticals)
     Section cross-reference(s): 1
FAN.CNT 1
     PATENT NO.          KIND   DATE        APPLICATION NO.         DATE
     --------------      ----   --------    --------------------    --------
PI   WO 2001009163        A2    20010208    WO 2000-GB2903          20000728 <--
     WO 2001009163        A3    20010907
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
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HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,
YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

GB 2355009 A1 20010411 GB 1999-17793 19990730 <--
AU 2000061739 A5 20010219 AU 2000-61739 20000728 <--
EP 1228093 A2 20020807 EP 2000-948177 20000728 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL
PRAI GB 1999-17793 A 19990730 <--
WO 2000-GB2903 W 20000728 <--

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2001009163	ICM	C07J
WO 2001009163	ECLA	A61K047/48H4; C07K014/47; C07K014/575; C07K014/595 <--
GB 2355009	ECLA	A61K047/48H4; C07K014/47; C07K014/575; C07K014/595 <--

OS MARPAT 134:168315

AB The present invention relates to improving and/or increasing the bioavailability of a biol. active substance, such as a peptide. In particular the present invention relates to the conjugation of the biol. active substance to a bile acid. The conjugated biol. active substance is suitable particularly for oral or parental administration. Illeal administration of 600μg/kg gastrin tetrapeptide conjugated to cholate resulted in a significant mean increase in gastric acid secretion of 1.84 μmol over a 3 h collection period, while no increase in acid secretion was noticed by administration of tetragastrin alone or with sep. cholate.

ST bioavailability enhancement peptide bile salt

IT Immunoglobulins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(A; enhancement of bioavailability of peptides with bile salts)

IT Immunoglobulins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(D; enhancement of bioavailability of peptides with bile salts)

IT Immunoglobulins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(E; enhancement of bioavailability of peptides with bile salts)

IT Immunoglobulins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(G; enhancement of bioavailability of peptides with bile salts)

IT Immunoglobulins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(M; enhancement of bioavailability of peptides with bile salts)

IT Chemotherapy
(agents; enhancement of bioavailability of peptides with bile salts)

IT Adrenoceptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antagonists; enhancement of bioavailability of peptides with bile salts)

IT Anemia (disease)
(antianemic factors; enhancement of bioavailability of peptides with bile salts)

IT Peptides, biological studies

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(conjugates; enhancement of bioavailability of peptides with bile salts)

IT Adrenoceptor agonists
Adrenoceptor antagonists
Analgesics
Anesthetics
Anti-inflammatory agents
Antianginal agents
Antiarrhythmics
Antibacterial agents
Anticoagulants
Anticonvulsants
Antidepressants
Antihistamines
Antiparkinsonian agents
Antipsychotics
Antiviral agents
Anxiolytics
Cardiotonics
Diuretics
Drug bioavailability
Fungicides
Hypnotics and Sedatives
Hypolipemic agents
Muscarinic agonists
Muscarinic antagonists
Nicotinic antagonists
Parasiticides
Permeation enhancers
Stomach
Vasodilators
(enhancement of bioavailability of peptides with bile salts)

IT Peptides, biological studies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(enhancement of bioavailability of peptides with bile salts)

IT Antibodies
Blood-coagulation factors
Ferritins
Glycoproteins, general, biological studies
Hemoglobins
Interferons
Oligonucleotides
Opioids
Polynucleotides
Polysaccharides, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(enhancement of bioavailability of peptides with bile salts)

IT Bile acids
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(enhancement of bioavailability of peptides with bile salts)

IT Bile salts
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(enhancement of bioavailability of peptides with bile salts)

IT Gastrointestinal motility
(gastric, drugs for treatment of; enhancement of bioavailability of peptides with bile salts)

IT Drug delivery systems
(oral; enhancement of bioavailability of peptides with bile salts)
IT Drug delivery systems
(parenterals; enhancement of bioavailability of peptides with bile salts)
IT Antiulcer agents
(peptic; enhancement of bioavailability of peptides with bile salts)
IT Neuropeptides
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(transmitters; enhancement of bioavailability of peptides with bile salts)
IT 9001-08-5D, inhibitor
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anticholinesterase; enhancement of bioavailability of peptides with bile salts)
IT 50-56-6, Oxytocin, biological studies 1393-25-5, Secretin 8001-27-2, Hirudin 9001-05-2, Catalase 9001-27-8, Factor viii 9001-28-9, Factor IX 9002-60-2, Acth, biological studies 9002-61-3, Chorionic gonadotropin 9002-64-6, Parathyroid hormone 9002-67-9, Luteinizing hormone 9002-68-0, Follicle stimulating hormone 9002-71-5, Thyroid stimulating hormone 9002-72-6, Somatotropin 9002-76-0, Gastrin 9004-10-8, Insulin, biological studies 9007-12-9, Calcitonin 9007-43-6, Cytochrome c, biological studies 9007-92-5, Glucagon, biological studies 9011-97-6, Cholecystokinin 9015-71-8, Corticotropin releasing hormone 9015-94-5, Renin, biological studies 9034-39-3, Growth hormone releasing hormone 9034-40-6, Gonadotropin releasing hormone 9038-70-4, Somatomedin 9039-53-6, Urokinase 9041-90-1, Angiotensin I 9054-89-1, Superoxide dismutase 9087-70-1, Aprotinin 11000-17-2, Antidiuretic hormone 11096-26-7, Erythropoietin 11128-99-7, Angiotensin II 24305-27-9, Thyrotropin releasing hormone 51110-01-1, Somatostatin 57285-09-3, Inhibin 59392-49-3, Gastric inhibitory peptide 67763-96-6, Igf1 67763-97-7, Igf2 80043-53-4, Gastrinreleasing peptide 85637-73-6, Atrial natriuretic hormone 89750-14-1, Glucagon-like peptide I 119418-04-1, Galanin 139639-23-9, Tissue plasminogen activator
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(enhancement of bioavailability of peptides with bile salts)
IT 79-14-1D, Glycolic acid, salts 81-24-3D, Taurocholic acid, salts 81-25-4, Cholic acid 83-44-3D, Deoxycholic acid, salts 128-13-2D, Ursodeoxycholic acid, salts 360-65-6D, Glycodeoxycholic acid, salts 474-25-9D, Chenodeoxycholic acid, salts 474-74-8D, Glycolithocholic acid, salts 516-35-8D, Taurochenodeoxycholic acid, salts 516-50-7D, Taurodeoxycholic acid, salts 516-90-5D, TAurolithocholic acid, salts 640-79-9D, Glycochenodeoxycholic acid, salts 14605-22-2D, Tauroursodeoxycholic acid, salts 63948-32-3 64480-66-6D, Glycoursodeoxycholic acid, salts 83381-47-9, Gastrin-34 I (rat) 171511-54-9 324753-46-0 325142-35-6
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(enhancement of bioavailability of peptides with bile salts)
IT 9003-99-0, Peroxidase
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(horseradish; enhancement of bioavailability of peptides with bile salts)
IT 9002-10-2, Tyrosinase
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(mushroom; enhancement of bioavailability of peptides with bile salts)
IT 9035-81-8, Trypsin inhibitor
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(soy bean; enhancement of bioavailability of peptides with bile salts)

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FILE LAST UPDATED: 21 JUN 2005 <20050621/UP>
MOST RECENT DERWENT UPDATE: 200539 <200539/DW>
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L4 ANSWER 1 OF 1 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2001-182932 [18] WPIX
DNC C2001-054613
TI Novel amide of bile salt which is conjugated to a biologically active substance useful for improving and/or increasing bioavailability of biologically active substance when administered orally or parenterally.
DC B04
IN LUCAS, M L; MORRISON, J D; WHEELER, S
PA (UNIU) UNIV GLASGOW; (LUCA-I) LUCAS M L; (MORR-I) MORRISON J D; (WHEE-I) WHEELER S
CYC 95
PI WO 2001009163 A2 20010208 (200118)* EN 28 C07J000-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
GB 2355009 A 20010411 (200122) C07K017-00
AU 2000061739 A 20010219 (200129) C07J000-00
EP 1228093 A2 20020807 (200259) EN C07K014-595
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
ADT WO 2001009163 A2 WO 2000-GB2903 20000728; GB 2355009 A GB 1999-17793 19990730; AU 2000061739 A AU 2000-61739 20000728; EP 1228093 A2 EP 2000-948177 20000728, WO 2000-GB2903 20000728

FDT AU 2000061739 A Based on WO 2001009163; EP 1228093 A2 Based on WO 2001009163

PRAI GB 1999-17793 19990730

IC ICM C07J000-00; C07K014-595; C07K017-00
ICS A61K038-04; A61K047-28; A61K047-48; C07K014-47; C07K014-575

AB WO 200109163 A UPAB: 20010402
NOVELTY - An amide of a bile acid/salt bonded by an amide bond to a peptide (I), is new.

DETAILED DESCRIPTION - An amide of a bile acid/salt bonded by an amide bond to a peptide of formula -X-Y (I), is new.

X = a peptide chain of at least four amino acids in length or comprise two or more cross-linked polypeptide chains; and

Y = OH, NH2, or a 1-6C ester group bonded to the terminal carboxy of the polypeptide chain.

INDEPENDENT CLAIMS are also included for:

(1) preparation of a pharmaceutical formulation involves bringing into association (I) and a carrier; and

(2) use of an amide of a bile acid/salt compound of formula (III) in the manufacture of a medicament suitable for parenteral administration.

R1-R5 = OH, H or 1-6C alkyl;

B' = -R6-CO-Z;

R6 = 2-6C alkylene; and

Z = a pharmaceutically active agent.

ACTIVITY - Anesthetic; tranquilizer; hypnotic; neuroleptic; antidepressant; anticonvulsant; antiparkinsonian; analgesic; neuroprotective; vasodilator; antianginal; cardiant; anticoagulant; antilipemic; antiinflammatory; antiulcer; bactericidal; virucidial; fungicidal; parasiticidal; antianemic.

MECHANISM OF ACTION - None given.

USE - (I) is useful for therapy and is useful in the manufacture of a medicament in a form suitable for oral administration.

ADVANTAGE - Conjugation of a pharmaceutically active substance to the bile acid via the carboxylic acid group of the bile acid results in improved uptake of the active substance into the blood stream when administered orally. The conjugated compound may also be administered parenterally at much lower doses than unconjugated form of the biologically active substance. The pharmacokinetics and/or bioavailability of a biologically active material are improved when a bile salt or acid-conjugated biologically active material is administered parenterally.

Experiments were carried out on male Wistar rats. After anesthetization the surgical procedures were carried out to allow incubation of the stomach at the pyloroduodenal junction after ligation of the esophagus to measure gastric acid secretion, cannulation of the terminal ileum and/or of the proximal jejunum distal to the ligament of Treitz for infusion of peptide hormones. Gastric acid secretion was measure by the following method. Gastrin tetrapeptide (G4) (Trp-Met-Asp-Phe amide) and cholate-Trp-Met-Asp-Phe amide conjugate (G4-CA), was used as the test substance. Experiments with gastrin tetrapeptide (G4) showed that biologically active G4 was not absorbed across the wall of the small intestine. In 6 experiments, ileal infusion of a large dose of G4 (2500 micro g kg-1 in 1.0 ml isotonic saline) actually resulted in a fall in the mean gastric acid level of 0.23 plus or minus 0.21 micro mol hr-1. Thus, it was demonstrated that G4 was not absorbed across the wall of the ileum. This lack of absorption of G4 was also confirmed for the upper jejunum. It was also to test whether G4-CA was absorbed from the small intestine: in this case, the relatively low dose of 600 micro g kg-1 G4-CA was injected intraileally. The first intravenous injection of G4-CA (15 micro g kg-1) caused a significant mean peak increase above baseline in total acidity of 0.64 plus or minus 0.26 micro mol 15 min-1 (P=0.017), while the second intravenous (i.v.) injection also caused significant increase of 0.72 plus or minus 0.26 micro mol 15 min-1 (P=0.003) of 17 rats, ileal administration of G4-CA (600 micro g kg-1) resulted in a significant mean increase in gastric acid secretion of 1.84 plus or minus 1.49 micro mol (P=0.045) over the 3 hour collection period. When the G4-CA was infused into the jejunum, no increase in gastric acid secretion occurred. Furthermore, when this

jejunal infusion was then followed after 3 hours by ileal infusion of G4-CA, gastric acid secretion was strongly stimulated. In 5 rats, infusion of G4-CA (600 micro g kg-1 in 1.0 ml) into the jejunum caused a significant mean reduction in gastric acid levels. When G4-CA (600 micro g kg-1) was subsequently injected intra-ileally, the gastric acid levels were significantly increased by 1.63 plus or minus 0.31 micro mol. These results demonstrated the absorption of G4-CA with biological activity preserved. Furthermore, the absorption did not occur from the jejunum but was specific to the ileum: this indicated a requirement for bile salt facilitated transport. Experiments with gastrin decapeptide (G10) also showed that when G10-CA was infused intra-ileally on the same molar basis as G4-CA (1000 micro g kg-1 in 1.0 ml), there was considerable stimulation of gastric acid secretion. This confirmed that longer peptides were transportable across the wall of the ileum.

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FS CPI

FA AB; GI; DCN

MC CPI: B01-D02; B04-B04H; B04-C01A; B04-C01G; B04-C02; B04-E01; B04-G01; B04-H06; B04-H07; B04-J01; B04-L01

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